

Article

# Characterization, Source and Risk of Pharmaceutically Active Compounds (PhACs) in the Snow Deposition Near Jiaozhou Bay, North China

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**Abstract:** The occurrence and distribution of 110 pharmaceutically active compounds (PhACs) were investigated in snow near Jiaozhou Bay (JZB), North China. All target substances were analyzed using solid phase extraction followed by liquid chromatography coupled to tandem mass spectrometry. A total of 38 compounds were detected for the first time in snow, including 23 antibiotics, eight hormones, three nonsteroidal anti-inflammatory drugs, two antipsychotics, one beta-adrenergic receptor and one hypoglycemic drug. The total concentration of PhACs in snow ranged from 52.80 ng/L to 1616.02 ng/L. The compounds found at the highest mean concentrations included tetracycline (125.81 ng/L), desacetylcefotaxime (17.73 ng/L), ronidazole (8.79 ng/L) and triamcinolone diacetate (2.84 ng/L). The contribution of PhACs in the vicinity of JZB to the PhACs in the snow is far greater than the contribution of those transmitted over a long distance. PhACs are mainly derived from drugs applied to local humans and animals. Based on the individual risk quotient (RQ) values, tetracycline poses high risks to the relevant aquatic organisms (algae and invertebrates). The rational application and scientific management of PhACs is an effective approach to reduce the ecological risks in JZB.

**Keywords:** PhACs; snow; ecological risk; Jiaozhou Bay (JZB)

## 1. Introduction

Pharmaceutically active compounds (PhACs) are widely used in human disease treatment, animal breeding, and aquaculture husbandry to prevent or treat human and animal diseases [1]. Antibiotics, analgesics, steroids, antidepressants, antipyretics, and stimulants are among the arrays of PhACs. However, PhACs are not entirely absorbed by organisms, and a major fraction is excreted in parent or metabolite form through urine and feces [2,3]. As emerging organic pollutants, PhACs in the environment can be toxic to certain aquatic organisms and induce antibiotic resistance due to their large production volumes, pseudo persistence, bioaccumulation, and potential ecotoxicity [4,5]. In addition, long-term exposure to low concentrations of PhACs brings about tremendous risks to both the ecological environment and humans. PhACs poison the microflora or lower organisms

with the same or similar target organ after entering the environment. The microflora and lower organisms are the basis of the ecological system; thus, the destruction of these components is devastating to the entire ecological system, may cause changes to the carbon recycling processes and the ecological environment, and eventually will impact the health of humans [6].

The PhACs in the environment have also recently attracted much attention throughout the world. PhAC contamination has been reported in many countries, such as Spain [7], the USA [8], Malaysia [9], Germany [10], Cyprus [11], France [12], Canada [13], and India [14]. However, few PhACs have been regulated as contaminants worldwide [13]. PhACs have been detected in different environmental samples, including rivers [15], lakes [16], wastewater [17], soils [18] and sediments [19]. However, the existence of PhACs in snow has not been reported. PhACs in the snow can enter the water and soil ecosystem directly or indirectly. Snowfall is an important way to remove organic pollutants from the air and constitutes an important source of organic pollutants in water [20]. In general, PhACs are designed to cause specific effects even at low concentrations, and long-term exposure to low doses of these compounds can cause adverse effects to ecosystems [6].

Jiaozhou Bay (JZB) (N35°38′–36°18′, E120°04′–120°23′) is a typical semi-enclosed bay that is surrounded by the city of Qingdao (Figure 1). The degree of water exchange in the bay is far lower than that in the open sea, and the bay is easily influenced by rainfall, snowfall, and terrestrial input from rivers [21,22]. The occurrence of quinolone antibiotics and ciprofloxacin has been reported in the seawater in this area, revealing that JZB is polluted by PhACs [23]. Therefore, 110 commonly used PhACs were selected for this study based on the known drugs used in China, including hormones, hypoglycemic substances, antibiotics, diazepam, nonsteroidal anti-inflammatory drugs, and antiviral drugs, to investigate the characterization and source of PhACs in the snow at nearshore locations in JZB in North China. In addition, the preliminary potential ecological risk was evaluated for those PhACs in JZB.

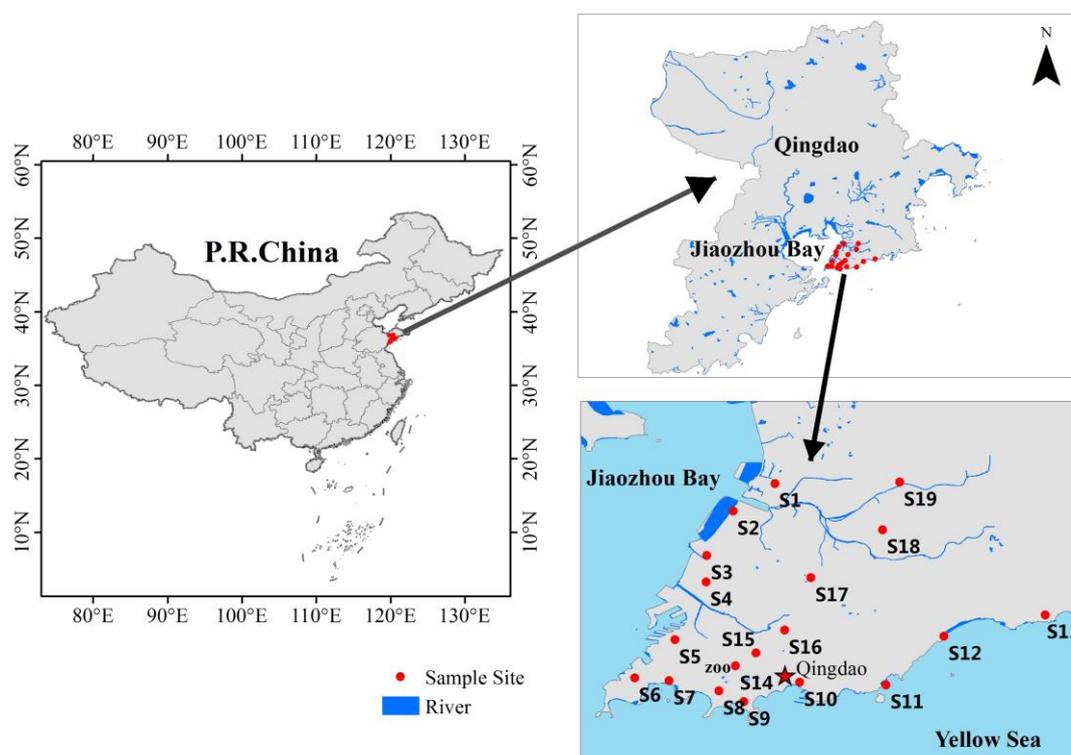


Figure 1. Locations of the sampling sites.

The results will help us gain insight into the chemical characteristics, source apportionment, and ecological risk of PhACs in the snow near JZB, and provide basic data support for further research on migration, transformation mechanisms, and other basic theoretical studies of PhACs.

## 2. Materials and Methods

### 2.1. Chemicals and Reagents

The compound names, CAS numbers and molecular formulas for all the target compounds are shown in Table S1 (Supplementary Materials). All standards were of high purity grade (>99%) and were purchased mainly from Anpel (Shanghai, China). All deuterated compounds were purchased from Anpel (Shanghai, China): Caffeine-D3 (CAF-D3), sulfamethoxazole-d4 (SUL-D4), norfloxacin-d5 (NOR-D5), ractopamine-d6 (RAC-D6), cimaterol-d7 (CIM-D7), and roxithromycin-D7 (ROX-D7). Acetonitrile (ACN) and methanol (MeOH) LC-MS grade were purchased from Fluka (Buchs, Switzerland) as well as formic acid (FA) 99%, while hydrochloric acid (HCl) 37% was obtained from Merck (Darmstadt, Germany). Ultrapure water (18.2 M $\Omega$ /cm quality) was supplied by a Millipore water purification system (Bedford, MA, USA). Oasis-HLB cartridges (200 mg/6 mL) were purchased from Waters (Milford, MA, USA), and GF/F glass-fiber membranes with a pore size of 0.7  $\mu$ m were provided by Whatman (Maidstone, England).

Approximately 10 mg of each individual standard was accurately weighed and placed in a 10 mL volumetric flask. All analytes were dissolved in acetonitrile–water mixtures (2:1, v/v). Stock solutions of 100.0 mg/L of each compound were obtained and stored at  $-80$  °C. From this multianalyte solution, all working solutions were prepared daily by appropriate dilution of the mixture stock standard (1.0 mg/L) and internal standard solutions (1.0 mg/L) in acetonitrile–water mixtures (2:1, v/v). The calibration standards were prepared by serial dilution of the mixed working solution using acetonitrile–water mixtures (2:1, v/v) with 0.1% v/v for mic acid resulting in individual concentrations ranging from 0.20 to 200  $\mu$ g/L.

### 2.2. Study Area and Sampling

JZB has an area of 367 square kilometers and is situated on the western coast of the Yellow Sea [21] and the eastern part of the Shandong Peninsula of China (Figure 1). The present study was carried out in the Qingdao area on 28 January 2018. The locations of the 19 sampling stations evaluated in this study are detailed in Figure 1.

As the prevailing wind directions in JZB are northwest (NW), the prevailing wind passed through the sampling site and over JZB during the sampling period (Figures 4 and 5). In addition, although the sampling stations were located downtown, there were no local PhAC sources nearby. According to the method of Wei et al. [24], 57 snow samples were collected from 19 sampling stations (three replicate samples were collected at each sampling station). Snow samples were decanted into 10.0 L pre-combusted (450 °C) dark-brown glass bottles, melted and acidified to pH (3.0  $\pm$  0.5) with 12 M HCl. The meltwater samples were vacuum filtered through GF/F glass-fiber membranes, and 0.5 L meltwater from each sample was stored in the dark at  $-20$  °C until analysis. Additional information, including the exact coordinates of the sampling stations and physicochemical parameters of the meltwater, is provided in Table S2.

### 2.3. Analytical Method

#### 2.3.1. Physicochemical Parameters

The ammonium, nitrites, nitrates, silicate, and phosphates were determined with a Quatro macro discrete autoanalyzer [25]. Total organic carbon (TOC) was analyzed using a 2100S element analyzer [26].

### 2.3.2. Pharmaceutically Active Compounds (PhACs)

The target compounds in the collected samples were analyzed following a procedure based on solid phase extraction (SPE) and ultrahigh-performance liquid chromatography combined with tandem mass spectrometry (UHPLC-MS/MS) [23]. The analytical methods in the study were described by Dasenaki et al. [27], but we optimized the methods in our laboratory. The optimized SPE procedure used Oasis-HLB cartridges (200 mg/6 mL) conditioned with 6 mL of methanol followed by 6 mL of ultrapure water. A total of 1.0 L of seawater was percolated through the cartridge under vacuum conditions (5 psi). Afterwards, the cartridge was rinsed with 10 mL of ultrapure water and then dried under vacuum conditions for 0.5 h to remove the excess water. Elution was performed with 10 mL of methanol. Extracts were evaporated under a gentle stream of nitrogen at 40 °C and reconstituted with 200 µL of acetonitrile–ultrapure water (30:70, v/v). Finally, 10 µL of a caffeine-D3 standard solution was added to obtain a final concentration of 10 µg/L in the extraction of the internal standard and analyzed by UHPLC-MS/MS.

Instrumental analysis was performed with a UHPLC-MS/MS system consisting of an AB SCIEX Triple Quad™ 4500 triple-quadrupole mass spectrometer (AB SCIEX Corporation, USA) equipped with an electrospray ionization source and a Shimadzu Nexera UHPLC system (Shimadzu Corporation, Kyoto, Japan), consisting of two solvent delivery modules LC-30 AD, a column oven CTO-30 AC, and an autosampler SIL-30AC. An Agilent Poroshell 120 EC-C18 column (4.6 mm × 150 mm, 2.7 µm) (Agilent, USA) was used. Optimized separation conditions were achieved using ultrapure water (0.01% FA (v/v) as solvent A and acetonitrile (0.01% FA (v/v) as solvent B at a flow rate of 400 µL/min. The gradient elution was performed as follows: Initial conditions, 5% B; 1–1.1 min, 5–15% B; 1.1–9.0 min, 15–75% B; 9.0–9.1 min, 75–95% B; 9.1–11.5 min, 95% B; 11.5–11.6 min, return to initial conditions; 11.6–15 min, equilibration of the column. The injection volume was 5 µL, and the column oven was set at 40 °C. The autosampler was operated at 8 °C. Analyses were performed in the positive mode for all compounds. The source temperature was 350 °C. Nitrogen was employed as the nebulizer gas (30 psi) and the dry gas (10 L/min), and the interface voltage was set at 5.5 kV. A mass spectrometer was operated in multiple reaction monitoring (MRM) mode, and two MRM transitions were monitored for each compound, with the most intense transition used as a quantifier and the other used as a qualifier. The MRM transitions for each compound were optimized by direct injection of individual standard solutions of each compound at 1 mg/L. A summary of individual MS/MS parameters is presented in Table S1.

### 2.4. Quality Assurance and Quality Control

The PhACs were identified by retention time and HPLC-MS/MS MRM mode, and the two ion transition pairs with the highest products were selected. The concentrations of the PhACs were computed using the internal standard method. A quality control sample (5 mg/L standards) was collected every five samples, followed by matrix spiked and blank samples. Calibration curves for the target analytes were drawn with eight points (0.5, 1, 5, 10, 20, 50, 100, and 200 µg/L), and the determination coefficients ( $R^2$ ) of the regression curves were >0.99 for each compound.

Recovery tests were performed by spiking with 1 µg/L PhACs standard to six select seawater samples. The recoveries ranged from 69% to 112%, and the RSD values ranged from 0.59% to 5.03%. The limits of detection (LODs) and limits of quantification (LOQs) for the instrument were defined as 3 and 10 times the signal-to-noise (S/N) ratios, respectively. The LOQs ranged from 0.06 to 2.3 ng/L, and all instrumental and procedural blanks were below the LOQs.

## 2.5. Risk Characterization

According to the European technical guidance document (TGD) [28], risk quotients (RQs) were applied to assess the potential ecological risks of PhACs using the following equation:

$$RQ = MEC/PNEC$$

$$PNEC = (LC_{50} \text{ or } EC_{50})/AF$$

where MEC denotes the measured concentration, and PNEC denotes the predicted no effect concentration. LC50 or EC50 denotes the half-maximal effective concentration (data from the literature is presented in Table S5), and AF is an assessment factor (100 for chronic toxicity, 1000 for acute toxicity). Three risk levels were established according to the different RQ values: High risk ( $RQ > 1$ ), medium risk ( $0.1 < RQ < 1$ ), and low risk ( $RQ < 0.1$ ) [29].

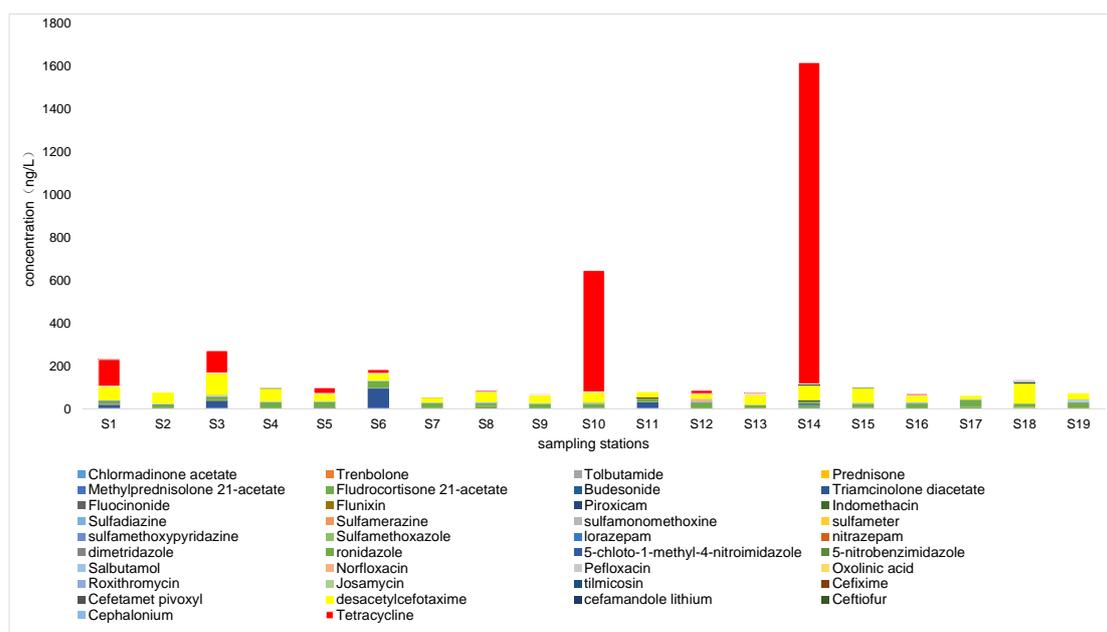
## 2.6. Statistical Analyses

Correlation tests were performed to investigate the overall correlation among the PhACs and between the individual PhACs and seawater physiochemical parameters included in Table S4. Linear regression analysis was used to assess the influence of environmental factors on the distribution of detected PhACs. A level of  $p < 0.05$  was considered statistically significant. Statistical analyses were performed using the statistical package SPSS (Window Version 18.0) and Statistica 10 software (StatSoft®, EUA).

## 3. Results and Discussion

### 3.1. Composition Characteristics of Pharmaceuticals in Snow

PhACs were found in all snow samples examined in the present study. The concentration levels, LOQ values, and detection frequencies of the detected target compounds are summarized in Table S3. The total concentration of PhACs in the snow sampled from the sampling sites near JZB ranged from 52.80 to 1616.02 ng/L (Figure 2), with an average concentration of 215.59 ng/L, which is higher than the concentration of PhACs in the seawater in JZB (54.82 ng/L) [23].



**Figure 2.** Cumulative levels of pharmaceutically active compounds (PhACs) at the different sampling stations.

A total of 38 target compounds were identified and quantified in the snow samples, with concentrations ranging from ND–1500.00 ng/L and LOQ values ranging from 0.1–2.3 ng/L. The highest concentrations of up to 1500.00 ng/L were observed for tetracycline. According to Figure 3a and Table S3, tetracycline (125.81 ng/L, 58.36%), desacetylcefotaxime (17.73 ng/L, 21.95%), ronidazole (8.79 ng/L, 8.22%) and triamcinolone diacetate (2.84 ng/L, 4.08%) were the preponderant PhACs. There were 14 substances (flunixin, sulfamonomethoxine, sulfameter, sulfamethoxy pyridazine, nitrazepam, ronidazole, 5-chloro-1-methyl-4-nitroimidazole, 5-nitrobenzimidazole, salbutamol, oxolinic acid, roxithromycin, desacetylcefotaxime, ceftiofur, and tetracycline) that showed frequencies of detection above 50%. Sulfamonomethoxine, sulfameter, sulfamethoxy pyridazine, nitrazepam, ronidazole, 5-chloro-1-methyl-4-nitroimidazole, 5-nitrobenzimidazole, salbutamol and desacetylcefotaxime were the most abundant compounds with detection frequencies of 100%, indicating that they were widespread in the snow of JZB. These results indicate that atmospheric deposition made a significant contribution to the migration and transportation of PhACs.

### 3.1.1. Antibiotics

Antibiotics are one of the most commonly used classes of pharmaceuticals and are commonly detected in marine environments [30,31]. China's shelf seas have been previously reported to be impacted by antibiotics [32]. In this study, 23 out of the 59 screened antibiotics were detected at the 19 sampling stations.

Six out of the 15 screened sulfonamides were detected: Sulfadiazine, sulfamerazine, sulfamonomethoxine, sulfameter, sulfamethoxy pyridazine, and sulfamethoxazole. The concentrations of sulfamonomethoxine, sulfameter, and sulfamethoxy pyridazine were above the LOQ in all samples with a frequency of detection of 100%, and these concentrations ranged from 0.55–0.58 ng/L, 0.45–2.17 ng/L, and 0.45–0.65 ng/L, respectively, indicating the widespread distribution of these compounds. Sulfadiazine and sulfamerazine were detected sporadically at low concentrations in the ranges of ND–0.20 and ND–0.08 ng/L, respectively. Sulfamethoxazole exhibited low detection frequencies of 5.26% and a maximum concentration of 3.95 ng/L. The mean concentrations of sulfadiazine and sulfamethoxazole in snow in this research were 0.08 and 0.21 ng/L, respectively, which are equivalent to the concentrations in the seawater of JZB [33] and lower than the concentrations in other surrounding sea areas, such as Laizhou Bay, Liaodong Bay, and Bohai Bay [34].

Three out of the 10 screened quinolones were detected: Norfloxacin, pefloxacin, and oxolinic acid. Oxolinic acid was detected with a frequency of detection of 52.63% in the range of ND–0.27 ng/L. Norfloxacin, along with pefloxacin, was detected at high levels (ND–11.50 and ND–6.43 ng/L, respectively) with a frequency of detection of 10.53%. Norfloxacin and pefloxacin are used primarily as human medicine, and their medical consumption is relatively high in China [35]. Norfloxacin and pefloxacin exhibited low concentrations and detection frequencies because they have short half-lives. We previously reported that the norfloxacin concentration in the seawater of JZB was within the range of ND–0.6 ng/L [23]. The norfloxacin concentration in the snow near the shore of JZB was higher than that in the seawater of JZB.

Three out of the 5 screened macrolides were detected: Roxithromycin, josamycin, and tilmicosin. Roxithromycin had a frequency of detection of 94.74% in the range of ND–0.60 ng/L, indicating its widespread distribution. Josamycin and tilmicosin were detected sporadically at low concentrations in the ranges of ND–0.11 and ND–2.64 ng/L, respectively. High levels of erythromycin and roxithromycin were determined by Minh et al. in the seawater of Victoria Harbour at concentrations up to 1900 and 47 ng/L, respectively [36]. The main reasons why the concentration of roxithromycin was lower in the snow sample from JZB than in the seawater may be the massive usage amount and relatively high boiling point of roxithromycin, which is a new generation of macrolide antibiotics and very difficult to volatilize in the natural environment. The concentration of josamycin in Tunisia coastal waters was measured to be 0.8 ng/L [37]. Josamycin and tilmicosin are rarely reported in seawater and have not been reported in the coastal waters of China.

Six out of the 15 screened cephalosporins were detected: Desacetylcefotaxime, cephalonium, cefixime, cefetamet pivoxyl, cefamandole, and ceftiofur. Desacetylcefotaxime and cephalonium were identified at frequencies of detection above 70% in the ranges of 16.20–101.00 and ND–5.61 ng/L, respectively. Desacetylcefotaxime mainly comes from the metabolism of cefotaxime; it has relatively weak antimicrobial activity, but its half-life period is longer and more stable than that of cefotaxime. Desacetylcefotaxime was the primary cephalosporin-contaminated drug in snow. The frequency of detection of cefixime, cefetamet pivoxyl, cefamandole, and cephalosporins was 5.26%, the mean concentration of ceftiofur was 1.43 ng/L, and the concentrations of the other three types were less than 1 ng/L. The six cephalosporins have been detected in different environmental media, such as milk [38], human blood [39], urine [40] and the effluents and influents of wastewater treatment plants (WWTPs) [33]. However, none of these substances have been previously identified in seawater samples.

Tetracycline was detected at high levels of up to 1500.00 ng/L with a frequency of detection of 63.16%, which is possibly the highest pollution concentration ever found in the water environment. We previously found tetracycline within the concentration range of ND–36.68 ng/L in JZB seawater [23]. The concentration of tetracycline in snow water measured in this study was 40 times higher than that in JZB seawater, which indicates that atmospheric sedimentation is important for the migration of tetracycline, and that the ocean is an important “sink” of tetracycline. Tetracycline commonly exists in the coastal waters of China, such as Victoria Harbour, Hong Kong (118 ng/L) [36], and Bohai Bay, China (270 ng/L) [34].

Four out of the 10 screened imidazoles were detected: Dimetridazole, ronidazole, 5-chloro-1-methyl-4-nitroimidazole, and 5-nitrobenzimidazole. Ronidazole, 5-chloro-1-methyl-4-nitroimidazole, and 5-nitrobenzimidazole had frequencies of detection of 100% in the ranges of 5.34–31 ng/L, 0.51–2.19 ng/L and 0.02–3.86 ng/L, respectively, indicating their widespread distribution. Ronidazole is an antimicrobial and anticoccidial drug and is mainly used for the prevention and treatment of histomoniasis and globidiosis in pets and wild birds [41]. Imidazoles and their metabolites may cause cancer and induce organism mutations [42]; thus, their use is strictly controlled, and these compounds have not been reported in JZB or the surrounding sea areas.

### 3.1.2. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are the most widely used pharmaceuticals for humans and animals due to their analgesic, antipyretic, and anti-inflammatory properties [43], and these compounds have been previously detected at high concentrations in treated wastewater from WWTPs [44]. In the NSAID group, only flunixin, piroxicam, and indomethacin were detected in the snow samples. Other compounds of this group with high rates of use, such as carprofen, diclofenac, ibuprofen, and trimethoprim [45], were not detected in any sample. This phenomenon may be associated with the physicochemical properties of these substances.

Flunixin presented a frequency of detection of 52.63% and was found in the range of ND–0.16 ng/L. Piroxicam, along with indomethacin, was detected at low levels (ND–0.16 and ND–3.19 ng/L, respectively), with a frequency of detection of 15.79%. High levels of piroxicam and indomethacin were observed by Collado Alsina in the effluent wastewaters from a WWTP in the range of 71–379 ng/L and 8–114 ng/L, respectively [46]. High levels of indomethacin up to 40 ng/L were detected by Walraven et al. in coastal surface water from the Netherlands [47]. NSAIDs have been extensively detected in seawater, surface water, and sewage waters worldwide [48]. The detection of these substances in the snow samples may be associated with the treatment efficiency of the sewage treatment plant.

### 3.1.3. Hormones

Hormone drugs can be used in combination with various types of antibacterial drugs to resist damage and calm or promote the relief of symptoms [49]. These hormones are widely used and soluble

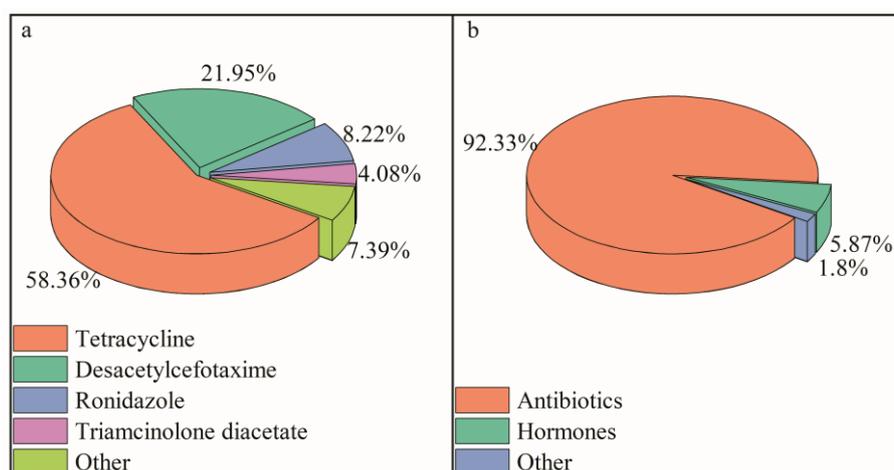
in water, so they exist at a high concentration in JZB. Eight out of the 20 screened hormones were detected: Prednisone, methylprednisolone acetate, fludrocortisone, budesonide, triamcinolone diacetate, fluocinonide, chlormadinone acetate, and trenbolone. The frequency of detection of all eight types of hormones in snow was very low (<50%). The average concentrations of these compounds except triamcinolone diacetate (8.79 ng/L) and fludrocortisone (2.06 ng/L) were all lower than 1.0 ng/L. Triamcinolone diacetate and fludrocortisone are widely used for the treatment of rheumatoid arthritis, bronchial asthma, atopic dermatitis, neurodermatitis, and eczema. High concentrations of hormones were observed in the effluents of a WWTP in Switzerland [50]. However, pollution by hormones in the sea areas around JZB has not been reported.

### 3.1.4. Other Pharmaceuticals

Out of the eight screened antipsychotic drugs, only lorazepam and nitrazepam were eventually detected. Lorazepam was detected only sporadically and was found in the range of ND–0.17 ng/L. Nitrazepam was found in the range of 0.21–0.35 ng/L with a high frequency of detection (100%). Nitrazepam was previously detected at a high mean concentration of 441 ng/L in the wastewater from the University Hospital of Santa Maria [51], which can explain its presence.

No  $\beta$ -adrenergic receptor drugs except salbutamol were detected. Salbutamol was detected in the snow samples at all sites, and the concentrations ranged from 0.10 to 6.85 ng/L. Only one out of the screened hypoglycemic drugs, tolbutamide, was detected. Tolbutamide presented a frequency of detection of 42.11% and was found in the range of ND–0.98 ng/L. The insolubility in water, low boiling point and easy volatilization in air of tolbutamide may be the reasons for its detection in snow.

According to the available literature, 38 detected target compounds were detected in accumulated snow for the first time. These compounds can be divided into six categories: Antibiotics, hormones, NSAIDs, hypoglycemic drugs, antipsychotic drugs, and  $\beta$ -adrenergic receptor drugs. Figure 3b shows that the majority of PhACs in the snow sample were antibiotics and hormones, accounting for 92.33% and 5.87%, respectively. Antibiotics and hormones are the most commonly used drugs in the medical and livestock breeding industries in China. These proportions are basically in accordance with the characteristics of production and application of PhACs in China.



**Figure 3.** Comparisons of the percentages of various PhACs in snow (a) each substance; (b) species.

## 3.2. Source Analysis

### 3.2.1. Path Source

The sources of contaminants in snow were mainly classified into local polluting source emissions and remote transmission of pollutants. The remote transmission of pollutants in this study was primarily impacted by the air mass coming from the northwest (Figure 4). The distribution of organic

pollutants in environments is affected by various factors such as  $\text{NH}_4\text{-N}$ ,  $\text{NO}_3\text{-N}$ ,  $\text{PO}_4\text{-P}$ ,  $\text{SiO}_3\text{-Si}$  and TOC [26]. To understand the relationship between environmental factors and the concentration of PhACs in snow, we analyzed the correlation. The results are shown in Table S4.

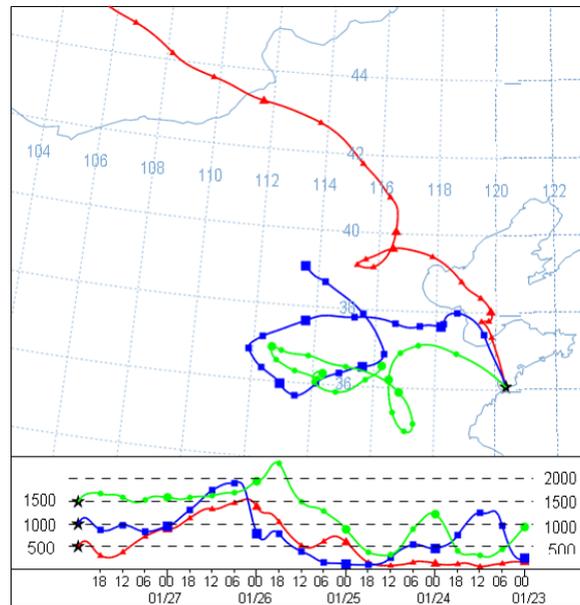


Figure 4. Typical air mass backward trajectories and their source directions during the sampling periods.

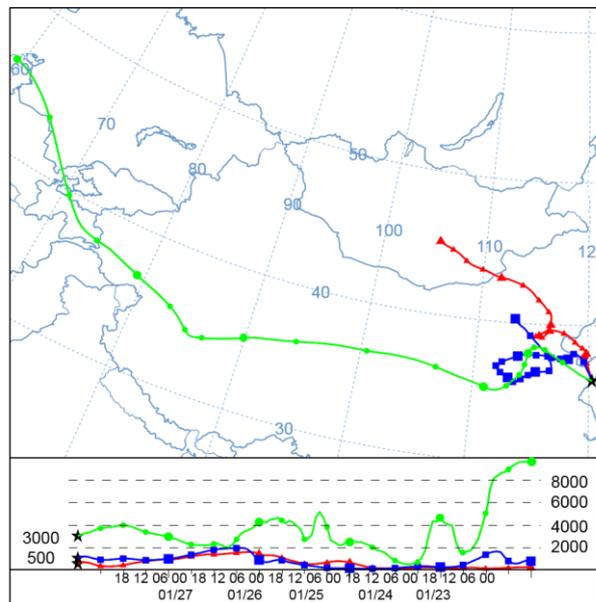


Figure 5. Source directions of typical precipitation air masses during the sampling periods.

Generally,  $\text{NH}_4\text{-N}$  mainly comes from agricultural activities [52,53], including volatilization of nitrogen fertilizer, animal husbandry, application of human and animal excreta, and other organic fertilizers [54,55], and the relatively high content of  $\text{NH}_4\text{-N}$  in snow is associated with the well-developed production of agriculture and animal husbandry near JZB [26].  $\text{NO}_3\text{-N}$  is considered to be closely associated with industrial and traffic emissions [56,57], and  $\text{NO}_3\text{-N}$  in snow is mainly in connection with well-developed local traffic and coal-fired heating in winter. The extremely remarkable positive correlation ( $p < 0.01$ ) among the  $\text{PO}_4\text{-P}$ ,  $\text{NO}_3\text{-N}$ , and  $\text{SiO}_3\text{-Si}$  concentrations indicated that they may have similar sources (local pollutant emission). The remarkable positive correlation ( $p < 0.05$ ) between TOC concentration and  $\text{SiO}_3\text{-Si}$  indicated that they may also

have similar sources. Thus,  $\text{NH}_4\text{-N}$ ,  $\text{NO}_3\text{-N}$ ,  $\text{PO}_4\text{-P}$ ,  $\text{SiO}_3\text{-Si}$  and TOC in snow were mainly local pollutant emissions.

As shown in Table S4, 14 kinds of PhACs (chlormadinone acetate, trenbolone, indomethacin, sulfamerazine, desacetylcefotaxime, sulfamonomethoxine, nitrazepam, tilmicosin, prednisone, budesonide, triamcinolone diacetate, sulfameter, lorazepam, and tetracycline) had a significant positive correlation with one or more environmental factors ( $\text{NH}_4\text{-N}$ ,  $\text{NO}_3\text{-N}$ ,  $\text{PO}_4\text{-P}$ ,  $\text{SiO}_3\text{-Si}$ , TOC) ( $p < 0.05$ ); thus, the 14 above-mentioned substances may come from local pollutant emissions.

There is a significant or extremely significant negative correlation between the substances of ronidazole and salbutamol and  $\text{NO}_3\text{-N}$ ,  $\text{PO}_4\text{-P}$ , and TOC ( $p < 0.05$  or  $p < 0.01$ ). Oxolinic acid shows a significant negative correlation with  $\text{NO}_3\text{-N}$  ( $p < 0.05$ ), and both salbutamol and ronidazole have a significant positive correlation with oxolinic acid ( $p < 0.05$ ). These results indicate that ronidazole, salbutamol, and oxolinic acid are not from local pollutant emissions but rather may be from remote transmission in the atmosphere. The backward trajectory chart of the air masses during the sampling period (Figure 4) shows that the airflow above JZB during the sampling period was mainly affected by the air masses coming from the northwest direction and the northwest desert area. The rainy cloud cluster was partially affected by the Loess Plateau in addition to the impact from the northwest cloud cluster (Figure 5). Therefore, Asian sand and dust particles brought strongly by winter northwest wind with low precipitation and dry weather increased the particle contents in the atmosphere and are beneficial to the adsorption of some PhACs with stable properties. In addition, due to the small molecular weight and stable properties of salbutamol, ronidazole, and oxolinic acid, these compounds can be easily adsorbed on particles for remote transmission.

### 3.2.2. Composition Source

The overuse of antibiotics, hormones, and other relevant drugs causes a rapid increase in PhACs in the environment. Determining the occurrence of PhACs in snow may help distinguish their possible sources. Multivariate linear regression (MLR) analysis together with principal component analysis (PCA) can be used to quantitatively evaluate the relative contribution of each PhAC from different sources to the total pollutants [58–61]. Therefore, PCA–MLR was adopted to assess the similarities and differences in PhAC distribution forms to deduce the possible sources of PhACs in snow. The concentrations of 11 principal PhACs (frequency of detection >50%) were taken as the active variables, and 19 samples were taken as the subjects. Three principal components (PC1, PC2, and PC3) were extracted with the eigenvalues >1 by PCA–MLR model, accounting for 63.89% of the total variance (Table 1).

According to the component matrix, the loadings of the different PhACs on the components are shown in Table 1. The first principal component (PC1) explained 30.98% of total variance with high loadings of sulfamonomethoxine, sulfameter, nitrazepam, ronidazole, salbutamol, desacetylcefotaxime, and ceftiofur. The results showed that PC1 was a factor of human drugs [62,63]. The second principal component (PC2) explained 17.97% of total variance, corresponding to the high loads of the veterinary drugs of flunixin, sulfamethoxazole, and tetracycline [64,65]. The third principal component (PC3) explained 14.94% of total variance, corresponding to the high loads of 5-nitrobenzimidazole, oxolinic acid, 5-chloro-1-methyl-4-nitroimidazole, and roxithromycin. PC3 denotes shared human–veterinary drugs [66,67]. MLR was then carried out on the factor scores of three identified components and  $\sum\text{PhACs}$  [68,69]. The regression equation is expressed as Equation (1):

$$\sum\text{PhACs} = 0.691 \text{ PC1} + 0.7915 \text{ PC2} + 0.238 \text{ PC3} \quad (R^2 = 0.951, p < 0.01). \quad (1)$$

The coefficients were set as  $B_i$ , and the contributions of each factor were calculated using Equation (2):

$$\text{Mean contribution of source, Percentage} = (B_i / \sum B_i) \times 100\% \quad (2)$$

**Table 1.** Loadings of PhACs on 3 components.

PhACs	Component		
	1	2	3
Sulfamonomethoxine	0.853	−0.239	−0.114
Sulfameter	0.891	−0.089	0.259
Nitrazepam	0.735	0.207	0.275
Ronidazole	−0.533	−0.162	0.33
Salbutamol	−0.575	−0.492	0.291
Desacetylcefotaxime	0.755	0.245	−0.223
Ceftiofur	0.858	−0.02	0.248
Flunixin	0.02	−0.675	0.198
Sulfamethoxazole	0.012	0.836	0.33
Tetracycline	0.101	0.832	0.227
5-chloto-1-methyl-4-nitroimidazole	−0.053	0.029	−0.76
5-nitrobenzimidazole	−0.12	−0.136	−0.726
Oxolinic acid	−0.376	−0.197	0.632
Roxithromycin	0.066	0.232	0.478
Eigenvalues	4.34	2.52	2.09
% Variance	30.98	17.97	14.94
Cumulative %	30.98	48.95	63.89

Extraction Method: Principal component analysis.  
Rotation Method: Varimax with Kaiser normalization.

The results showed that the contribution of PC1 to the total PhAC concentration in snow was calculated as 40.16%, while PC2 and PC3 contributed 46.00% and 13.83%, respectively. In other words, the drugs applied to humans, animals, or both humans and animals accounted for 40.16%, 46.00%, and 13.83% of the total PhACs, respectively. The proportion of medicine for humans and animals was relatively high in the snow sampled from the sampling sites near JZB. Therefore, the most effective methods to reduce PhACs in snow in JZB are to intensify the management of drugs used for humans and animals, improve the PhAC treatment capacities of sewage treatment plants, and scientifically dispose of animal waste.

### 3.3. Environmental Risk Assessment

In this study, the MECs and PNECs of the target compounds for algae, invertebrates, plants, and fish were utilized to conduct a risk assessment. According to the most sensitive PNEC values, the RQs were calculated using the maximum MECs, and the results of the risk assessment are presented in Table S5 and Figure 6. The concentration levels of the compounds detected in this study do not pose a toxic effect on either plants or fish because all their RQs were far lower than 0.1. However, invertebrates and algae are sensitive to PhACs in aquatic environments. The RQ value of tetracycline to invertebrates was as high as 35.97, indicating that tetracycline may cause very high ecological risks to relevant invertebrates. The situation is also not pleasant in terms of algae; The RQ values of tetracycline and sulfamethoxazole to algae were 16.67 and 0.13, respectively, referring to high and medium risks.

Algae and invertebrates are an important component to the bottom of the food chain, and minor changes in the population structure will have a significant impact on the entire ecosystem [70]. Therefore, we should conduct long-term monitoring and effective management of PhACs in the environment. The actual ecological risk of PhACs in snow may be higher than the reported data. There are two reasons for this: First, different types of PhACs in the marine environment do not exist alone. Due to the limitations of basic toxicological data, this study discussed the RQ values of only PhACs, and it is not possible to accurately estimate the cumulative toxicity risk of various PhACs. Second, because most of the PhACs evaluated in this study were new types of marine organic

pollutants, some of the target toxicity data were unknown; as a result, we are temporarily ignoring their ecological risk.

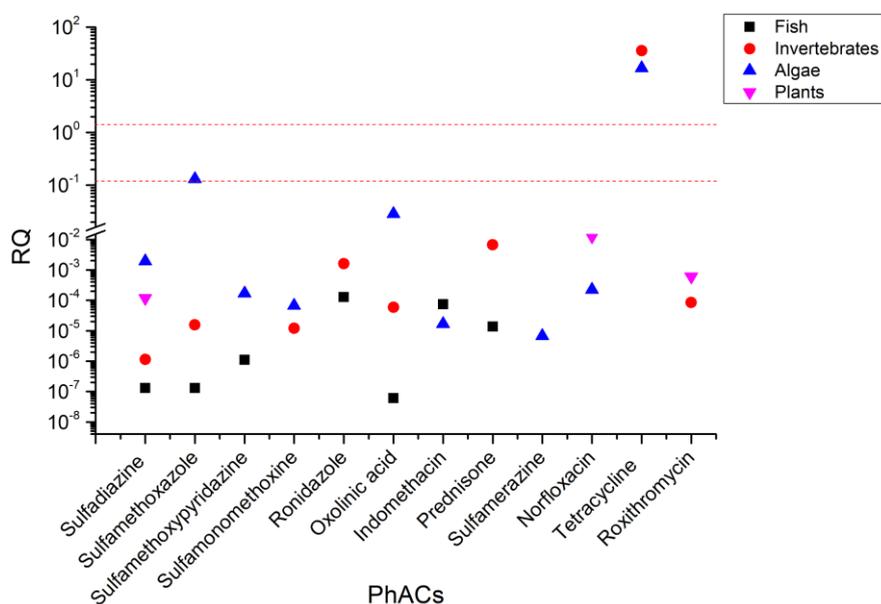


Figure 6. Risk quotients (RQs) for the PhACs detected in the surface seawater of JZB.

#### 4. Conclusions

In this study, the occurrence and distribution of 110 PhACs in snow near the JZB were investigated for the first time, and the possible sources and potential risks were estimated. A total of 38 substances were detected in snow with concentrations at the ng/L level, including sulfadiazine, sulfamerazine, sulfamonomethoxine, sulfameter, sulfamethoxyipyridazine, sulfamethoxazole, norfloxacin, pefloxacin, oxolinic acid, roxithromycin, josamycin, tilmicosin, cefixime, cefetamet pivoxyl, desacetylcefotaxime, cefamandole, ceftiofur, cephalonium, tetracycline, dimetridazole, ronidazole, 5-chloro-1-methyl-4-nitroimidazole, 5-nitrobenzimidazole, flunixin, piroxicam, indomethacin, tolbutamide, prednisone, methylprednisolone 21-acetate, fludrocortisone 21-acetate, budesonide, triamcinolone diacetate, fluocinonide, chlormadinone acetate, trenbolone, lorazepam, nitrazepam, and salbutamol. All these contaminants were detected for the first time in snow. Antibiotics (92.33%) and hormones (5.87%) were the dominant compounds in JZB snow. Snow deposition has a direct scavenging effect on air pollutants. As a whole, the PhACs concentration in snow at JZB was higher than that in the seawater of JZB. Additionally, snowfall can effectively remove PhAC pollutants in the atmosphere and has an important significance in adjusting the PhAC concentration in the air. The residual PhACs in the snow in JZB mainly come from local pollutant emissions in Qingdao, followed by remote transmission of PhACs. A total of 14 PhACs (chlormadinone acetate, trenbolone, indomethacin, sulfamerazine, desacetylcefotaxime, sulfamonomethoxine, nitrazepam, tilmicosin, prednisone, budesonide, triamcinolone diacetate, sulfameter, lorazepam, and tetracycline) came from local pollutant emissions, while salbutamol, ronidazole, and oxolinic acid came from remote transmission. The results of PCA-MLR source analysis show that the proportions of the drugs used for animals and humans in the accumulated snow samples in JZB to the snow samples at all JZB offshore sampling points were relatively high, at 46.00% and 40.16%, respectively. An environmental risk assessment revealed that tetracycline could present high ecological risk to relevant algae and invertebrates, and sulfamethoxazole might pose a medium risk to algae. Therefore, we need to strengthen the control of the use of human and veterinary drugs, improve the capacities of sewage treatment plants to process drug residue, and process animal excrements in a more scientific way, with the goal of decreasing the concentrations of human medicines and veterinary drugs in the environment.

**Supplementary Materials:** The following are available online at <http://www.mdpi.com/2076-3417/9/6/1078/s1>.

**Author Contributions:** J.S. and Q.P. conceived and designed the experiments; Q.P., X.L., H.Y., and G.Y. performed the experiments and analyzed the data; Q.P. and J.S. wrote the manuscript; all authors discussed the results and edited the manuscript.

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